ADVERSE EFFECTS OF ANTIRETROVIRAL AGENTS (Updated January 10, 2011)

Adverse effects have been reported with all antiretroviral (ARV) drugs and are among the most common reasons for switching or discontinuing therapy as well as for medication nonadherence *[1]*. Rates of treatment-limiting adverse events in antiretroviral therapy (ART)-naïve patients enrolled in randomized trials appear to be declining with newer ARV regimens and are generally now less than 10%. However, most clinical trials have a relatively short follow-up duration and can underestimate longer term complications of therapy. In the Swiss Cohort study, the presence of laboratory adverse events was associated with higher rates of mortality during 6 years of follow-up, highlighting the importance of adverse events in overall patient management *[2]*.

Several factors may predispose individuals to adverse effects of ARV medications. For example, women seem to have a higher propensity of developing Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine (NVP) (ART-naïve women with CD4 counts >250 cells/mm^3) *[3-5]* as well as higher rates of lactic acidosis from nucleoside reverse transcriptase inhibitors (NRTIs) *[6-8]*. Other factors may also contribute to the development of adverse events: concomitant use of medications with overlapping and additive toxicities; comorbid conditions that may increase the risk of or exacerbate adverse effects (e.g., alcoholism *[9]* or coinfection with viral hepatitis, which may increase risk of hepatotoxicity *[10-12]*); drug-drug interactions that may lead to an increase in dose-related toxicities (e.g., concomitant use of ribavirin with didanosine [ddI], which may increase ddI-associated toxicities) *[13-15]*); or genetic factors predisposing patients to abacavir (ABC) hypersensitivity reaction *[16-17]*.

Although the therapeutic goals of ART include achieving and maintaining viral suppression and improving patient immune function, an overarching goal should be to select a regimen that not is only effective but also is safe. This requires consideration of not only the toxicity potential of an ARV regimen but also an individual patient's underlying conditions, concomitant medications, and history of drug intolerance.

Information on adverse events is outlined in multiple tables in the guidelines:

Table 13 provides clinicians with a list of the most common and/or severe known ARV-associated adverse events listed by drug class. **Appendix B, Tables 1–6** summarize the most common adverse effects of individual ARV agents. Some approaches to the management of complications of ART have been published and will not be discussed in these tables *[18-21]*.

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (January 10, 2011)

(See Appendix B for additional information listed by drug.)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding events			**All PIs:** ↑ spontaneous bleeding, hematuria in hemophilia **TPV:** Reports of intracranial hemorrhage. Risks include CNS lesions; trauma; surgery; hypertension; alcohol abuse; coagulopathy, anti-coagulant, or anti-platelet agents including vitamin E		
Bone marrow suppression	**ZDV:** Anemia, neutropenia				
Cardiovascular disease (CVD)	**ABC** and **ddI:** Associated with myocardial infarction (MI) in some but not all cohort studies. Risk greatest among those with traditional CVD risk factors.		**PIs:** Associated with MI and stroke in some cohort studies. Risk greatest among those with traditional CVD risk factors. Limited data on newer PIs (ATV, DRV, TPV). **SQV/r**, **ATV/r,** and **LPV/r:** PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and coadministration with drugs that prolong PR interval. **SQV/r:** QT interval prolongation in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG prior to SQV initiation is recommended and should be considered during therapy.		
Central nervous system (CNS) effects	**d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)	**EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Most symptoms subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and ↑ plasma EFV concentrations due to genetic factors or absorption (i.e., with food).			
Diabetes mellitus (DM)/insulin resistance	**ZDV, d4T,** and **ddI**		• Reported for some **PIs (IDV, LPV/r**), but not all PIs studied • **ATV** +/- **RTV** not found to alter insulin sensitivity		
Dyslipidemia	**d4T > ZDV > ABC:** • ↑ LDL and TG	**EFV** • ↑TG • ↑LDL	↑LDL, ↑TG, ↑HDL: **all RTV-boosted PIs** ↑TG: **LPV/r = FPV/r** and **LPV/r > DRV/r** and		

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Diabetes mellitus (DM)/insulin resistance	**ZDV, d4T,** and **ddI**		• Reported for some **PIs (IDV, LPV/r)**, but not all PIs studied • **ATV** +/- **RTV** not found to alter insulin sensitivity		
Dyslipidemia	**d4T > ZDV > ABC:** • ↑ LDL and TG	**EFV** • ↑TG • ↑LDL • ↑HDL	↑LDL, ↑TG, ↑HDL: **all RTV-boosted PIs** ↑TG: **LPV/r** = **FPV/r** and **LPV/r** > **DRV/r** and **ATV/r**		
Gastrointestinal (GI)	Nausea and vomiting: **ddI** and **ZDV** > other **NRTIs** Pancreatitis: **ddI**		GI intolerance (diarrhea, nausea, vomiting) Diarrhea: common with **NFV**. **LPV/r** > **DRV/r** and **ATV/r**		

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	Lipoatrophy: **Thymidine analogs (d4T > ZDV).** May be more likely when combined with **EFV** vs. **boosted PI**.	Lipohypertophy: Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens; however, causal relationship has not been established.			
Myopathy/elevated CPK	**ZDV:** myopathy			**RAL:** ↑ CPK. muscle weakness and rhabdomyolysis	
Nephrotoxicity/ urolithiasis	**TDF:** ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis Concurrent use of **PI** may increase risk.		**IDV**: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy **IDV, ATV**: Stone, crystal formation; adequate hydration may reduce risk.		
Osteopenia/ osteoporosis	**TDF:** Associated with greater loss of bone mineral density (BMD) compared with **ZDV, d4T,** and **ABC.**	Decreases in BMD observed in studies of regimens containing different **NRTIs** combined with either **NNRTIs** or **PIs**.			
Peripheral neuropathy	Peripheral neuropathy (pain and/or paresthesias, lower extremities > upper extremities): **d4T > ddI** and **ddC** (can be irreversible) **d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)				
Rash		**All NNRTIs**	**ATV, DRV, FPV**		**MVC**
Stevens-Johnson syndrome (SJS)/ toxic epidermal necrosis (TEN)	**ddI, ZDV:** Reported cases	**NVP > DLV, EFV, ETR** For **NVP** risks include: •Female sex	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases		

Acronyms:
Drug Classes: EI = entry inhibitor; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PIs = protease inhibitor
Antiretroviral Drugs: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir + ritonavir; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delaviridine; DRV = darunavir; DRV/r = darunavir + ritonavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir + ritonavir; FTC = emtricitabine; IDV = indinavir; LPV/r = lopinavir + ritonavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir + ritonavir; TDF = tenofovir; TPV = tipranavir; ZDV = zidovudine
Other: ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; BMD = bone mineral density; CNS = central nervous system; CPK = creatine phosphokinase; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; LDL = low-density lipoprotein; MI = myocardial infarction; PT = prothrombin time; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrosis; TG = triglyceride

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